European Journal of Obstetrics & Gynecology and Reproductive Biology 170 (2013) 348–351

Contents lists available at SciVerse ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Ischemia-modified albumin in pregnancy

Alberto Rossi [a], Nadia Bortolotti [b], Sara Vescovo [b], Irene Romanello [a,*], Leonardo Forzano [a], Ambrogio Pietro Londero [a], Guido Ambrosini [c], Diego Marchesoni [a], Francesco Curcio [b]

[a] Obstetrics and Gynecology Department, University Hospital of Udine, Udine, Italy
[b] Clinical Analysis Institute, University Hospital of Udine, Udine, Italy
[c] Department of Obstetrics and Gynecology, University of Padua, Italy

ARTICLE INFO

Article history:
Received 26 October 2012
Received in revised form 26 May 2013
Accepted 28 June 2013

Keywords:
Ischemia-modified albumin
Trophoblast development
Fetal growth restriction
Oxidative stress

ABSTRACT

Objective: In normal pregnancies, a hypoxic intrauterine environment seems necessary for early trophoblast development. In this context, maternal serum levels of ischemia-modified albumin (IMA) are elevated, reflecting the oxidative stress associated with placental development. The aim of this study was to evaluate IMA and pregnancy-associated plasma protein A (PAPP-A) in mothers bearing small-for-gestational-age (SGA) fetuses compared to normal pregnancies.
Study design: A prospective study was performed between June 2010 and June 2011. Serum total albumin, IMA and PAPP-A concentrations were determined in 81 pregnant women in three different periods: 1st trimester, 2nd trimester and postpartum. Two groups of subjects were retrospectively identified: Group (1) mothers bearing appropriate-for-gestational-age (AGA) fetuses, and Group (2) mothers bearing SGA fetuses. Serum total albumin and IMA concentrations were determined in 198 non-pregnant women as controls.
Results: Serum IMA concentrations increase during gestation. IMA/albumin serum levels in the 1st trimester were significantly higher in subjects of Group (2) ($p < 0.05$), whereas values of serum PAPP-A MoM were significantly lower ($p < 0.05$).
Conclusions: Elevated IMA serum levels together with low levels of PAPP-A were detected in the 1st trimester in mothers bearing SGA fetuses, and this may reflect early placental changes occurring before clinical manifestation of SGA.

1. Introduction

Ischemia-modified albumin (IMA) has emerged as a sensitive biomarker in the evaluation of ischemia-based acute coronary syndromes, thus improving the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia [1–6]. Ischemic events and the subsequent myocardial reperfusion are advocated to be the pathogenic mechanism responsible for the presence of IMA. In this context, the albumin molecule undergoes oxidative modifications on its amino terminal portion, thus losing its ability to bind metal cations such as Co^{2+} [7,8]. The ischemia-reperfusion events trigger biochemical environmental changes globally known as "oxidative stress", defined as an imbalance between pro-oxidant and antioxidant substances, resulting from either increased production of oxidants or decreased antioxidant properties, or a combination of both [9].

Recent studies show that serum levels of IMA are physiologically increased during normal pregnancies, and that first-trimester maternal IMA levels are well above the cut-off used to diagnose cardiac ischemia [10–13]. On the other hand, it is known that early fetal organogenesis occurs in a low-oxygen environment, probably because of the limitation of maternal-fetal oxygen transfer due to the gestational sac [14]. Elevated maternal serum IMA levels support the hypothesis that mild hypoxia and subsequent reperfusion occurring during normal placentation determine the onset of oxidative stress [15,16]. Increased IMA serum levels have been detected in patients with pre-eclampsia or fetal growth restriction (FGR) as a consequence of defective trophoblast invasion [17,18]. In this case, maternal spiral arterioles retain their vasoreactivity leading to poorer placental blood perfusion with hypoxia: the subsequent reperfusion-related injury is thought to predispose to the development of preeclampsia [19]. In the present study, attention was focused on mothers bearing small-for-gestational-age (SGA) fetuses.

* Corresponding author at: Department of Obstetrics and Gynecology, University Hospital of Udine, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy. Tel.: +39 347 9115998.
E-mail address: irenerom@libero.it (I. Romanello).

0301-2115/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejogrb.2013.06.037

A newborn with a birth weight below the 10th centile is considered to have been a small-for-gestational-age fetus; this is a heterogeneous group, including those fetuses who have failed to achieve their growth potential after fetal growth restriction (FGR), and those who are constitutionally small. SGA fetuses are at risk of increased perinatal mortality, complications such as stillbirth and birth hypoxia, and finally impaired neurodevelopment [20].

Different markers of oxidative stress have been considered in the pathogenesis of FGR, suggesting that reactive oxygen species (ROS) could play a role [21]. Evidence [22–25] suggests that low levels of pregnancy-associated plasma protein A (PAPP-A), a known high molecular-mass glycoprotein synthesized by the syncytiotrophoblast and typically measured at 11–13 weeks of gestation for screening of common aneuploidies, is associated with a variety of serious adverse perinatal outcomes related to placental insufficiency. The aim of this study was to examine IMA and PAPP-A as markers of oxidative stress in pregnancies with small-for-gestational-age (SGA) fetuses and in normal pregnancies.

2. Materials and methods

A prospective study was carried out at the University Hospital of Udine between June 2010 and June 2011. Eighty-one women with singleton pregnancies who came to the Obstetrics and Gynecology Clinic for nuchal translucency screening, for the 20–22 weeks scan, and for delivery were enrolled. Women suffering from any current or pre-existing medical or obstetrical diseases, those with multiple pregnancies, and mothers bearing fetuses affected by fetal malformations or chromosomal defects were excluded. All the women enrolled were aged between 18 and 40 years.

Each woman underwent three venous blood samples at different time points. The first blood sampling was between 11 and 14 weeks of gestation (T1), when nuchal translucency was performed. The second was carried out at the time of the standard second trimester scan and uterine artery Doppler examination between 19 and 22 weeks of gestation (T2). The third was performed within 2 h after delivery (T3). The T1 and T2 samples were taken in the morning after an overnight fast of 8 h.

PAPP-A was measured only at the first time point whereas serum total albumin and IMA were measured at all three time points. Serum specimens were frozen at −20 °C or colder within 2 h: after thawing they were gently vortexed and immediately analyzed.

According to the outcome, pregnant women were divided into two groups: Group (1) ($n = 65$), mothers bearing appropriate-for-gestational age (AGA) fetuses, and Group (2) ($n = 16$) mothers bearing small-for-gestational-age (SGA) fetuses: each newborn with a birth weight below the 10th centile was considered SGA. As a control group, 198 non-pregnant healthy women were examined, all of them aged between 18 and 40 years.

Total albumin concentration was measured by the instrument Modular P from Roche Diagnostics using the albumin reagent BCG.

IMA concentration was measured by the instrument ILAB 300 from Instrumentation Laboratory using a previously described method by which the cobalt not bound by the modified albumin was detected. IMA concentrations were expressed as Absorbance units (ABSU) $\times 10^3$, and total albumin concentrations were expressed as g/dL. To compare the results of each patient taking into account the different serum albumin levels, IMA values were divided by the respective values of total albumin and IMA/albumin Units were reported.

PAPP-A was measured by the instrument Kryptor from Brahms GmbH using the reagent Brahms PAPP-A Kriptor. The intra-assay repeatability was 5%, according to the manufacturer cut off.

Data were analyzed using R (version 2.14.0) [26] and $p < 0.05$ was considered significant. Normality of variables was tested with the Kolmogorov–Smirnov test. Non-parametric data were presented with the median value and the interquartile range (IQR), whereas parametric data were described with the mean value and its standard deviation.

For bivariate analysis, the following statistical tests were applied: the Wilcoxon test, *t*-test, linear regression, and Kendall's tau for continuous variables and the Chi-square and Fisher exact test for categorical variables.

The study was approved by the local Ethics Committee and written consent was obtained from all the participants before entry into the study.

Table 1
Demographic characteristics of the 81 pregnant women recruited.

	AGA	SGA	*p*
Mean maternal age, years (±SD)	31.2 (±4.5)	31.9 (±1.7)	0.362
Gestational age, weeks (±SD)	38.8 (±1.5)	39.6 (±0.6)	<0.05*
Spontaneous delivery %	55% (36/65)	44% (7/16)	0.398
Operative delivery %	14% (9/65)	6% (1/16)	0.398
Cesarean section %	31% (20/65)	50% (8/16)	0.160
UA bilateral notch 20 weeks %	9% (6/65)	44% (7/16)	<0.05*

* $p < 0.05$.

Table 2
Placental and neonatal characteristics in the immediate post-partum.

	AGA	SGA	*p*
Placental index (±SD)	0.18 (±0.03)	0.16 (±0.01)	<0.05*
Neonatal weight (g) (±SD)	3270.4 (±405)	2891.25 (±154.9)	<0.05*
Neonatal weight MoM (±SD)	1.0 (±0.1)	0.8 (±0.0)	<0.05*
Apgar score 1st minute (±SD)	8.5 (±1.0)	8.5 (±0.5)	0.797
Apgar score 5th minute (±SD)	9.0 (±0.5)	9.00 (±0.0)	0.621

* $p < 0.05$.

3. Results

The mean age of the mothers enrolled in the study was 31.4 years (±4.1); none of them was a smoker. The average age of the non-pregnant women was 25 years (±6.2), significantly different from that of the case study group ($p < 0.05$). Table 1 shows the demographic characteristics of the women involved, including mean maternal age, the percentage of spontaneous deliveries, operative deliveries, cesarean sections and the presence of bilateral notch at the Doppler flow analysis of maternal uterine arteries. The prevalence of bilateral notch is significantly higher in mothers bearing SGA fetuses. Table 2 shows the weight at birth, both in grams and MoMs, the

Table 3
IMA/albumin ratio in SGA and AGA groups in the 1st trimester (T1), in the 2nd trimester (T2) and in the post-partum (T3).

	AGA	SGA	*p*
IMA/albumin T1 ABSU $\times 10^3$/g/dL (±SD)	1161.4 (±211.2)	1278.6 (±171.2)	<0.05*
IMA/albumin T2 ABSU $\times 10^3$/g/dL (±SD)	1868.1 (±476.1)	1675.8 (±216.8)	<0.05*
IMA/albumin T3 ABSU $\times 10^3$/g/dL (±SD)	2514.2 (±589.5)	2045.5 (±358.5)	0.291
IMA/albumin T2-T1 ABSU $\times 10^3$/g/dL (±SD)	706.7 (±425.7)	397.2 (±303.5)	<0.05*
IMA/albumin T3-T1 ABSU $\times 10^3$/g/dL (±SD)	1346.3 (±574.0)	885 (±200.8)	0.118

* $p < 0.05$.